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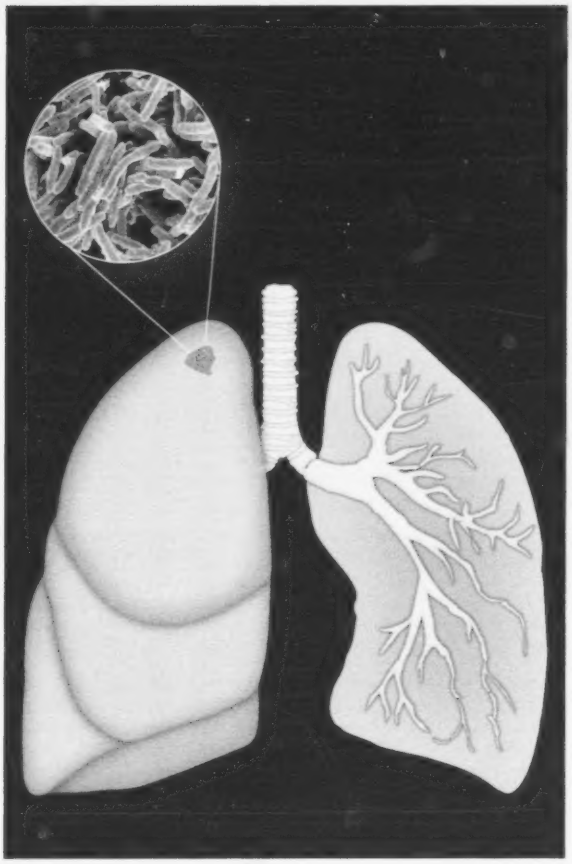
CCDR

CANADA COMMUNICABLE DISEASE REPORT

TUBERCULOSIS (TB)



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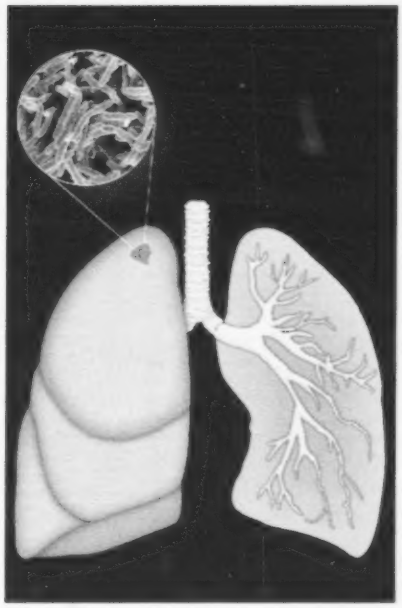

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OVERVIEW

Latent tuberculosis infection: An overview

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Abstract

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis (TB) disease. Individuals with LTBI represent a reservoir for active TB cases. The detection and management of LTBI is now a key component of the World Health Organization's End TB Strategy and the Government of Canada's federal framework for action on TB prevention and control. This is because people with LTBI can progress to active TB or undergo reactivation, a risk that is greatly increased in those with immunocompromising conditions. This overview provides a summary of LTBI and reactivation risk, as well as the recent advances in the diagnosis and treatment of LTBI.

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Introduction

Tuberculosis (TB) is a leading cause of death worldwide, with 10.4 million cases and 1.8 million deaths in 2015 (1). Infected individuals are classified as either having latent tuberculosis infection (LTBI), an asymptomatic clinical state that is not transmissible, or active TB disease, characterized by the presence of clinical symptoms arising from infection that can occur in multiple organs. While *Mycobacterium tuberculosis*, the bacterium that causes TB, can infect many parts of the body, pulmonary TB is primarily the transmissible form. Our understanding of *M. tuberculosis* infection as a clear binary condition that is either active or latent has recently shifted, and the more modern view treats infection as a spectrum of disease states (2).

The World Health Organization's (WHO) End TB Strategy has set the goal to reduce TB incidence globally by 90% and TB deaths by 95% by 2035 (3). While active TB case detection has been the cornerstone of the public health response to TB, modelling suggests that in order to reach these ambitious targets, reducing the LTBI reservoir through preventative therapy is essential (3,4). Preventing the progression of LTBI to active TB disease is an important public health goal that can substantially reduce TB transmission. A key part of the End TB Strategy is targeted treatment of those infected and who are at risk for progression to active TB disease.

The objective of this paper is to summarize what we know about LTBI, including the risk factors for reactivation, recent advances in diagnosis and treatment, and next steps in advancing the global plans for TB elimination.

Latent tuberculosis infection and reactivation

The WHO defines LTBI as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB (5). According to recent estimates, approximately one-quarter of the global population is infected with LTBI (6). The duration of latency is variable, and healthy individuals can harbour LTBI for a lifetime. In a small fraction (~5%–15%), reactivation occurs, often within the first 2 to 5 years following infection (7,8). Reactivation is the process by which a subclinical latent infection transitions into active TB disease. Thus, individuals with LTBI represent a major reservoir for new active TB cases (9).

The understanding of the underlying reasons for LTBI reactivation is incomplete, but it does include bacterial, host and environmental factors (10). While the lifetime risk for reactivation among otherwise healthy individuals with documented LTBI is quoted as approximately 5% to 15% (7,8), various comorbidities and risk factors are associated with increased risk and hence elevated rates of developing active TB. The most potent risk factor is human immunodeficiency virus (HIV) infection. Those with HIV and latent TB co-infection have more than a 100-fold increased risk of developing active TB disease (11). Even after successful antiretroviral therapy, the risk remains significantly elevated (12,13). Other comorbidities and conditions associated with LTBI reactivation are categorized as high, moderate, slightly increased, low and very low risk, depending on their associated risk factors (14). In the high-risk category are patients with chronic renal failure requiring hemodialysis (15), transplant patients on immune suppressants (16) and patients with silicosis (17), among others. At moderate risk are patients treated with tumour necrosis factor alpha (TNF-α) inhibitors (used for many autoimmune and inflammatory conditions) (18) or glucocorticoids (19), those with diabetes (all types) and recently infected children under the age of four (20). Those who abuse alcohol (21), smoke cigarettes (22) or are underweight or malnourished (23) are at slightly increased risk for LTBI reactivation. TB incidence is higher among these groups than within the general population (14). A commonality among the majority of these conditions leading to increased reactivation risk is suppressed immunity.

LTBI treatment

TB reactivation rates can be substantially reduced by up to 90%, if LTBI patients take preventative therapy (24,25). The major indications for LTBI therapy are recent infection or the presence of other factors for increased risk for TB reactivation as noted above. The standard treatment regimen is nine months of daily self-administered isoniazid (INH9), although a 6-month course is also acceptable but not preferred due to reduced efficacy (14). Due to the length of treatment, and hepatotoxicity-related side effects, adherence is a major issue affecting therapy completion. The 3- to 4-month daily isoniazid plus rifampin regimen is authorized for use in Canada as an alternative, as is the 4-month daily rifampin regimen (14). Recently, a 12-dose once-weekly regimen of isoniazid plus rifapentine (commonly known as 3HP), administered by directly observed therapy, has been shown to be as effective as the standard INH9, and has also resulted in reduced hepatotoxicity and higher compliance rates (26). Currently rifapentine is not authorized for use in Canada and is only available through Health Canada's Special Access Program. For more information on the 3HP regimen, see Pease et al. in this issue (27).

LTBI diagnostics

The effective delivery of preventative therapies relies on sensitive and accurate LTBI diagnosis to guide treatment delivery. While bacterial culture is the gold standard for the diagnosis of an active infection, there remains no such standard for the detection of LTBI (28). Since detection of the actual pathogen is not possible, LTBI is detected by measuring immune responses to *M. tuberculosis* antigens.

Two tests currently measure immune responses to *M. tuberculosis* antigens: the tuberculin skin test (TST), which dates back over 100 years, and the more recent interferon-gamma release assay (IGRA) (28,29). The TST evaluates cell-mediated immunity and consists of the intradermal injection of a small amount of purified protein derivative from the *M. tuberculosis* bacteria. The test requires two patient visits with a 48–72 hour interval between the administration and reading of the test. It is open to considerable variation in the interpretation of results.

The IGRA is a whole blood–based in vitro assay that measures the production of interferon-gamma by immune cells in response to *M. tuberculosis* antigen stimulation. The test does not require that the patient return to the lab and can be completed in 24 hours, but it does require greater laboratory infrastructure and technical capacity, which means it is more expensive. The specificity of the IGRA is superior to the TST as it utilizes antigens found only in *M. tuberculosis*, thereby eliminating cross-reactivity with the Bacille Calmette-Guerin (BCG) vaccine strain that is still routinely used in many countries, including Canada in some high TB-burden northern communities (14,28). There are two IGRA platforms currently available in Canada. The QuantiFERON-Gold In-Tube test is based on an enzyme-linked immunosorbent assay (ELISA) for the detection of interferon-gamma production in separated plasma. The T.SPOT.TB test is an enzyme-linked immunospot (ELISPOT) assay based on the enumeration of interferon-gamma producing immune cells; it requires lymphocyte separation, stimulation and culture.

The *Canadian Tuberculosis Standards* recommend the use of either TST or IGRA for LTBI diagnosis (14). Only those who would benefit from treatment, including those at high risk for reactivation, should be tested. The IGRA is the preferred test in individuals who have had a BCG vaccine after infancy or in groups with poor return rates for TST reading (14). The TST is recommended if repeat testing is planned (14). Neither test should be used to screen those at low risk for infection or progression, to diagnose active TB or to monitor TB treatment response.

Because the TST and IGRA rely on the detection of a specific immune response, both tests have reduced sensitivity among immunocompromised populations, leading to high levels of false-negative results. This includes those who are HIV infected, where test sensitivity decreases with loss of CD4 T cell counts (30,31), and patients with end stage renal disease (32). Unfortunately, it is these same groups that have the highest risk for LTBI reactivation and require accurate testing and treatment.

New LTBI diagnostics

The development of new diagnostics for LTBI has been slow, but some recent advances include a skin test, C-Tb, that utilizes *M. tuberculosis*–specific antigens similar to those used in the IGRA assays, eliminating cross-reactivity with the BCG vaccine while maintaining sensitivity of the existing TST assay (33). The latest generation of the Quantiferon test has also been recently released. The QuantiFERON-TB Gold Plus assay incorporates new antigens designed to increase test sensitivity among immunocompromised groups, including people living with HIV. The initial independent evaluations, however, have shown this new test to have minimal increased sensitivity (34). Variations of the IGRA test that utilize alternate immune readouts in response to TB antigen stimulation are also being explored. One such readout is the cytokine IP-10, produced at much higher levels than interferon-gamma. Use of such a readout could both increase test sensitivity, particularly in immunocompromised groups, as well as reduce time to detection, bringing the test closer to true point of care testing (35).

In addition to sensitivity issues, neither the TST nor the IGRA can accurately distinguish active TB disease from LTBI, and neither can predict LTBI reactivation (29,35,36). There is a need for advancements to be made in the LTBI diagnostics field to develop improved tools for diagnosing LTBI and predicting LTBI reactivation. A more sophisticated understanding of the immunology of LTBI and the underlying factors associated with progression to active disease is critical to identifying new biomarkers or immune signatures that will form the basis of new LTBI diagnostics and tools to monitor the success of therapeutic regimens. A promising advance in this direction is a 16-gene messenger RNA transcript-signature in blood that predicts subsequent disease progression and is able to distinguish between latent infection and active TB disease (37). In addition, it seems to be associated with bacterial burden as the immune transcript-signature was lost following TB treatment. Development of diagnostic tests that can identify those most at risk for reactivation and development of TB disease could help

guide interventional strategies to target those most at risk for reactivation and therefore most in need of preventative therapy.

The strategy to eliminate tuberculosis

For countries such as Canada who have already reached the End TB target milestones (<100 TB cases/million), an action framework was created by WHO to reach TB elimination targets (<1 TB case/million) by 2050 (38). This framework was designed recognizing that in low incidence countries, TB transmission is infrequent within the general population, and aside from occasional outbreaks, most cases of active TB are due to reactivation of LTBI (9,39).

In 2015, the WHO published guidelines on testing, treating and managing LTBI in infected individuals with the highest likelihood of progression to active disease (5). These guidelines call for a targeted public health approach that includes screening of select groups at high risk for LTBI reactivation coupled with preventative treatment in those who will most benefit from it (40,41). Target groups include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor treatment, patients receiving dialysis, patients preparing for transplantation and patients with silicosis. Other vulnerable and/or hard-to-reach groups with a higher incidence of TB disease include those in correctional facilities, those with drug and alcohol addictions, people dealing with homelessness, residents of long-term care facilities, Indigenous populations, and migrants from countries with a high TB burden. For these high-risk groups, systematic testing is recommended in countries where resources are available. Both the IGRA and TST are recommended tools for screening, and chest radiography should be performed prior to initiating LTBI therapy to rule out active TB disease. Patients taking LTBI treatment should also be monitored regularly for potential adverse side effects (5).

Elements of the WHO guidelines are being implemented in Canada, and the identification and treatment of LTBI among those at high risk for developing active TB disease is a key area of focus as outlined in the Government of Canada's federal framework for action on TB prevention and control (42). The *Canadian Tuberculosis Standards*, developed by the Canadian Thoracic Society and the Public Health Agency of Canada, recommend the targeted screening of groups identified as at increased risk for LTBI reactivation, similar to those groups outlined in the WHO LTBI management guidelines (14). As these targeted screening and treatment approaches are likely to be led mainly by primary care providers, it is important that physicians are informed of LTBI screening and management policies in order to recognize risk factors. The most important factors to consider when selecting people as suitable candidates for LTBI screening and treatment are their risk of prior TB exposure and for reactivation balanced against the risk for hepatotoxicity, and the likelihood of treatment completion.

Conclusion

The reactivation of TB from untreated LTBI is a major source of new active TB infections and transmission. It accounts for the majority of new tuberculosis cases in countries where the incidence of tuberculosis is low, such as Canada. In order to meet TB elimination goals, targeted LTBI testing and treatment of marginalized and hard-to-access groups and those with high risk for TB reactivation is a priority. Shorter and efficacious preventative treatment regimens, more sensitive LTBI diagnostics and novel tests to identify those individuals at the highest risk for TB reactivation will all help to reach the TB elimination goals.

Conflict of Interest

None.

Contributions

SK: conceptualization, preparation of original draft, review and editing. TBB: conceptualization, review and editing.

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A shorter treatment regimen for latent tuberculosis infection holds promise for at-risk Canadians

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Abstract

Despite recent success in reducing its incidence, tuberculosis remains a considerable challenge in Canada, particularly among foreign-born and Indigenous populations. A key component of the strategy for controlling the disease is the treatment of latent tuberculosis infection (LTBI). The standard treatment consists of isoniazid (INH) daily for nine months. In recent years, shorter regimens have been developed in the hope of increasing rates of treatment acceptance and completion. Of these, the shortest and most recently developed is a combination of INH and rifapentine taken once weekly for 12 doses (3HP), typically using directly observed therapy. This regimen has been approved by the Food and Drug Administration in the United States but is not yet authorized for use in Canada.

Based on a rapidly expanding number of observational studies and randomized controlled trials, 12 weeks of 3HP appears to have similar efficacy to nine months of INH, a favourable adverse event profile and potentially improved rates of treatment completion. Although rates of treatment acceptance, the role of self-administered therapy and the regimen's cost-effectiveness within the Canadian context remain uncertain, 3HP is a promising alternative to existing treatments for LTBI.

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Introduction

Although the incidence of active tuberculosis (TB) in Canada has gradually declined over the past decade, the disease remains a major health challenge that disproportionately affects marginalized populations (1). The burden of the disease—90% of active cases—falls on the foreign-born populations and Canadian-born Indigenous people (1). In 2014, 69% of reported new cases of active TB in Canada occurred in the migrant population where the incidence rate was 13.7/100,000 (1). Among First Nations, who comprise the majority of Canadian-born Indigenous people, the incidence rate was even higher at 19.3/100,000 (1). However, the highest rate of active TB in Canada was reported among the Inuit, with an incidence of 198.3/100,000, a rate over 300 times that of the Canadian-born, non-Indigenous population (1). In fact, this rate is similar to that of the TB burden in developing countries such as Afghanistan, Ethiopia and Bangladesh (2).

The World Health Organization has set an ambitious strategy to end the global TB epidemic by 2035. They defined the end as reaching a global incidence rate of fewer than 100 cases per million population (3). A vital component of the overall approach to eliminating TB is reliable testing and effective treatment of latent tuberculosis infection (LTBI) to prevent active disease in at-risk populations (3). LTBI occurs when individuals are exposed to infectious active TB and their immune system sequesters viable *Mycobacterium tuberculosis* bacilli but does not lead to active disease (4). While neither infectious nor symptomatic, those with LTBI carry a 5%–15% lifetime risk of developing active TB from reactivation of the sequestered bacilli (5). Clinically, LTBI is diagnosed by either a positive tuberculin skin test (TST) or a positive interferon-gamma release assay (IGRA), in the absence of active disease (6). Although neither of these tests represent a gold standard, they are the recommended tests for the diagnosis of LTBI in Canada (6).

Treatment of latent TB infection

Treatment of those with LTBI reduces the risk of developing active disease by 60%–90% (7), which in turn prevents ongoing transmission (8). Although treatment efficacy in preventing active TB is one important aspect in the selection of a treatment regimen, it is not the only factor to consider. The goal of therapy is to reduce the individual risk of developing active TB and to reduce TB transmission within populations. Other important considerations include anticipated rates of acceptance (the proportion of those offered treatment who initiate the treatment) and completion (the proportion of those who accept treatment who finish the treatment). Adverse effects are also of central importance, particularly since LTBI treatment is usually given to healthy patients in the hopes of preventing disease. Finally, the cost effectiveness of the regimen in comparison to other competing interventions must be evaluated.

The current international and Canadian standard for the treatment of LTBI is nine months of daily isoniazid (INH9) (6). However, the prolonged duration of this treatment may hinder completion of therapy (9). One shorter-course option is rifampin (RMP) given daily for four months. This regimen has been shown to be as safe as INH9 and to improve the adherence rate, but its effectiveness is less well established (10,11). A multicentre, multinational randomized controlled trial to be completed shortly compares the effectiveness of RMP and INH9 (12). Another alternative is a combination of INH and RMP given daily for 3–4 months. This regimen likely has a safety and efficacy profile similar to INH-based regimens (13,14).

However, even these shorter-course regimens require adherence to daily therapy for several months. A newly developed regimen consists of a combination of INH and rifapentine given once weekly for 12 doses (3HP). Rifapentine was initially developed as a treatment for active TB in the 1970s and early 1980s (15), but its use by HIV patients for the continuation phase of active TB treatment demonstrated rates of treatment resistance higher than that of rifampin (16). As such, rifapentine is not recommended for use in active TB in Canada (17). Nonetheless, it is an effective short-course treatment option that requires by far the fewest doses of any regimen. This regimen was recently approved for the treatment of LTBI by the United States Food and Drug Administration but it is not yet authorized for use in Canada.

Treatment efficacy

The first randomized controlled trial (RCT) to evaluate 3HP for LTBI was published in 2006 (18), over 20 years after the development of rifapentine (15). As with other more recent RCTs, 3HP was tested using directly observed therapy (DOT) (18-21). This trial, which compared 3HP to a regimen of two months of daily RMP and pyrazinamide, showed comparable efficacy in preventing active TB and lower rates of adverse effects with 3HP (18). Note that RMP/pyrazinamide is no longer recommended for LTBI treatment because of the increased risk of severe liver injury and death compared to INH (6). A subsequent trial conducted in HIV patients showed the efficacy of 3HP, INH given for six months, INH given continuously for up to six years and a combination of INH and RMP given for 12 weeks to be comparable (19). These findings prompted the PREVENT TB trial, a large multicentre non-inferiority RCT that compared directly observed 3HP and self-administered INH9 (20). The trial included nearly 4,000 patients per arm and demonstrated the non-inferiority of 3HP compared to INH9 (20). To the best of our knowledge, no trials comparing self-administered 3HP to INH9 have been published. A follow-up study to the PREVENT TB trial that focused on the pediatric population showed similar results (21). Furthermore, a 2013 Cochrane review (22) and a recent network meta-analysis support the efficacy of 3HP (14). An earlier network meta-analysis published in 2014 did not find a statistically significant benefit of 3HP in preventing active TB compared to other regimens, but interpretation of this study is complicated by the inclusion of numerous studies that did not confirm LTBI (23).

Treatment acceptance and completion

Because acceptance of treatment cannot accurately be determined in randomized trials (given that patients accept entry into the trial rather than a specific regimen), data are limited to observational studies. Unfortunately, rates of treatment acceptance are often low. In a study of all the patients who tested positive for LTBI in Tennessee between 2002 and 2006, only 53% of those offered treatment began taking it and only 54% of those who started treatment completed it (24). Furthermore, a recent meta-analysis of 58 studies, mainly from high-income countries and published between 1946 and 2015, showed that only about 30% of those with LTBI who were offered treatment started it and only 18.8% completed treatment (25). In addition, the meta-analysis estimated an acceptance rate of 62% for treatment regimens consisting of isoniazid monotherapy (25). The included studies involved a variety of treatment regimens and took place in a range of populations including contacts of patients with active TB, marginalized populations, migrants and the general population (25).

A 2016 study by the New York City Health Department found the acceptance rate of 3HP to be 302/503 (60%) with 92/503 (18%) choosing other treatments and the remainder refusing all treatment (26). The overall rate of treatment acceptance was similar to that previously recorded in the clinic (historical control), which had predominantly offered INH9 (26). Among those who opted for other therapies, the requirement for DOT in the clinic was the reason most often cited for declining 3HP (26).

Improving treatment completion rates is a key goal of the shorter-course regimens. In the 2006 RCT by Schechter et al., completion of both 3HP and RMP/pyrazinamide was approximately 93% (18). Martinson et al. reported a completion rate of 95.7% for 3HP, which was higher than comparator regimens (19). In the PREVENT TB trial, 82% of patients completed therapy in the 3HP arm compared to 69% of those in the INH9 arm ($P<0.001$) (27). Risk factors for non-completion included experiencing an adverse event, substance use and a history of incarceration (27). A network meta-analysis of RCTs found higher rates of completion for 3HP and INH/RMP compared to INH monotherapy (14).

Observational studies have also supported improved completion rates with the 3HP regimen. In New York City Health Department TB clinics, 196/302 (65%) of patients completed their regimen of 3HP compared to 42/92 (46%) who opted for other treatment ($P<0.01$) which was higher than the 34% in historical controls ($P<0.01$) (26). Among those incarcerated in California, 77/91 (85%) patients completed 3HP compared to 28/154 (18%) who completed INH9 (28). In an observational study at an American community health centre, 35/45 (78%) of patients in the 3HP arm and 49/94 (52%) of patients in the INH9 arm completed treatment ($P=0.005$) (29). The degree to which higher completion rates are driven by the use of DOT remains unclear.

Adverse events

Adverse events are another crucial component of LTBI treatment regimen selection. The PREVENT TB trial reported high rates of broadly defined hypersensitivity reactions with 3HP (20). However, the definition of such reactions was wide-ranging, including a combination of some 17 possible clinical criteria, and the severity of these reactions was not initially defined (20). Based on concerns about such reactions, the *Canadian Tuberculosis Standards* recommends the regimen be used only under closely monitored circumstances (6). In 2015, Sterling

et al. published a more detailed analysis of the adverse events in the PREVENT TB trial, clarifying this issue (30). Systemic drug reactions were more common in the 3HP regimen than the INH9 regimen, with rates of 138/3,893 (3.5%) and 15/3,659 (0.4%), respectively ($P<0.001$) (30). However, these reactions were mostly a flu-like syndrome (63%) and cutaneous reactions (17%) (30). Severe reactions were rare (0.3%) and were associated with concomitant medications and White race (30). No patient developed anaphylaxis and no deaths were attributable to medication (30).

Reporting of adverse events was limited in early trials of 3HP (18,19). However, rates of hepatotoxicity among patients taking 3HP have been lower than comparators in all RCTs (18-21). In the PREVENT TB trial, 18/4,040 (0.4%) patients in the 3HP arm versus 103/3,759 (2.7%) in the INH9 arm developed hepatotoxicity (20). An unpublished post-marketing study monitoring 2,134 patients taking 3HP in the United States found the side effect profile to be similar to that in the PREVENT TB trial (20,31). Fevers and chills were reported in 126/2,134 (6%) and myalgia or arthralgia in 148/2,134 (7%) (31). Hepatotoxicity occurred at a rate of 10/2,134 (0.5%). In an incarcerated population, 5/91 (5.5%) developed transient fever and chills (28). A recent systematic review of the adverse events associated with 3HP found that rates of adverse events of this regimen compared favourably to those of other LTBI treatments but with higher rates of flu-like reactions and less hepatotoxicity (32). A comparison of INH9 and 3HP is summarized in **Table 1**.

Table 1: The treatment schedule, acceptance, completion and adverse event rates of isoniazid (INH) and INH plus rifapentine (3HP)

Drug	Dosing schedule	Observed?	Acceptance rate	Completion Rate	Rate of systemic drug reactions	Hepatotoxicity
Isoniazid (INH9)	Daily dose for 9 months	No. Self-administered	62%[1] (26)	18-69% (27-30)	0.4% (31)	2.7% (20)
INH+ rifapentine (3HP)[2]	Weekly dose for 12 weeks	Yes. Directly observed treatment.	60% (27)	65%-95% (18,19, 27-30)	3.5% (31)	0.4% (20)

[1] Some patients represented in this estimate were offered INH for six or 12 months rather than nine months.
[2] Note: The 3HP treatment regime is not yet authorized for use in Canada.

Treatment cost-effectiveness

To our knowledge, the cost-effectiveness of 3HP in Canada has not yet been evaluated. A 2013 cost-effectiveness analysis in the United States found that over 20 years 3HP cost an additional US$4,294 to $21,525 per TB case prevented and an additional US$911 to $4,565 per quality-adjusted life year than INH9 (33). However, an update incorporating new, lower prices for rifapentine substantially altered this evaluation and, in fact, demonstrated cost savings compared to the price of INH9 (34). A recent study from Taiwan also demonstrated cost savings (35). However, differences in health systems, geography and local economic factors make generalization of cost-effectiveness studies between countries difficult (36). This highlights the need for high quality cost-effectiveness studies of LTBI treatment specific to the Canadian context.

Conclusion

While TB remains a challenge in Canada, particularly among foreign-born and Indigenous populations, newer regimens offer expanded options for the treatment of LTBI. Compared to the standard regimen of daily INH for nine months, a regimen of the more recent 3HP is shorter, equally effective, with improved completion rates and a generally favourable adverse effect profile. However, uncertainty remains with respect to acceptance and completion rates given the current use in the DOT setting as well as the role for self-administered therapy and the impact of the regimen in remote communities. The cost-effectiveness within the Canadian context has not been established. Several ongoing trials will help to answer these questions. A study comparing the adherence to self-administered versus directly observed 3HP has been completed (37), but not yet reported. The Taima TB: 3HP study, which is currently recruiting in Iqaluit, Nunavut, will examine the acceptance and completion rates of 3HP versus those of the 9-month, twice weekly INH regimen that is standard in the territory (38). A trial in Ottawa will attempt to compare the acceptance and completion of 3HP and INH9 in an urban Canadian setting with a high proportion of foreign-born residents. Such trials will help to clarify the optimal role of the 3HP regimen, in anticipation of the regimen's authorization for use in Canada.

Conflict of interest

Dr. Alvarez is the principal investigator of the Taima TB 3HP study in Iqaluit and Ottawa. Dr. Amaratunga is the site investigator for the Ottawa arm of the Taima TB 3HP study.

Contributions

Authors: GGA, CP, KRA wrote, reviewed and edited the manuscript.

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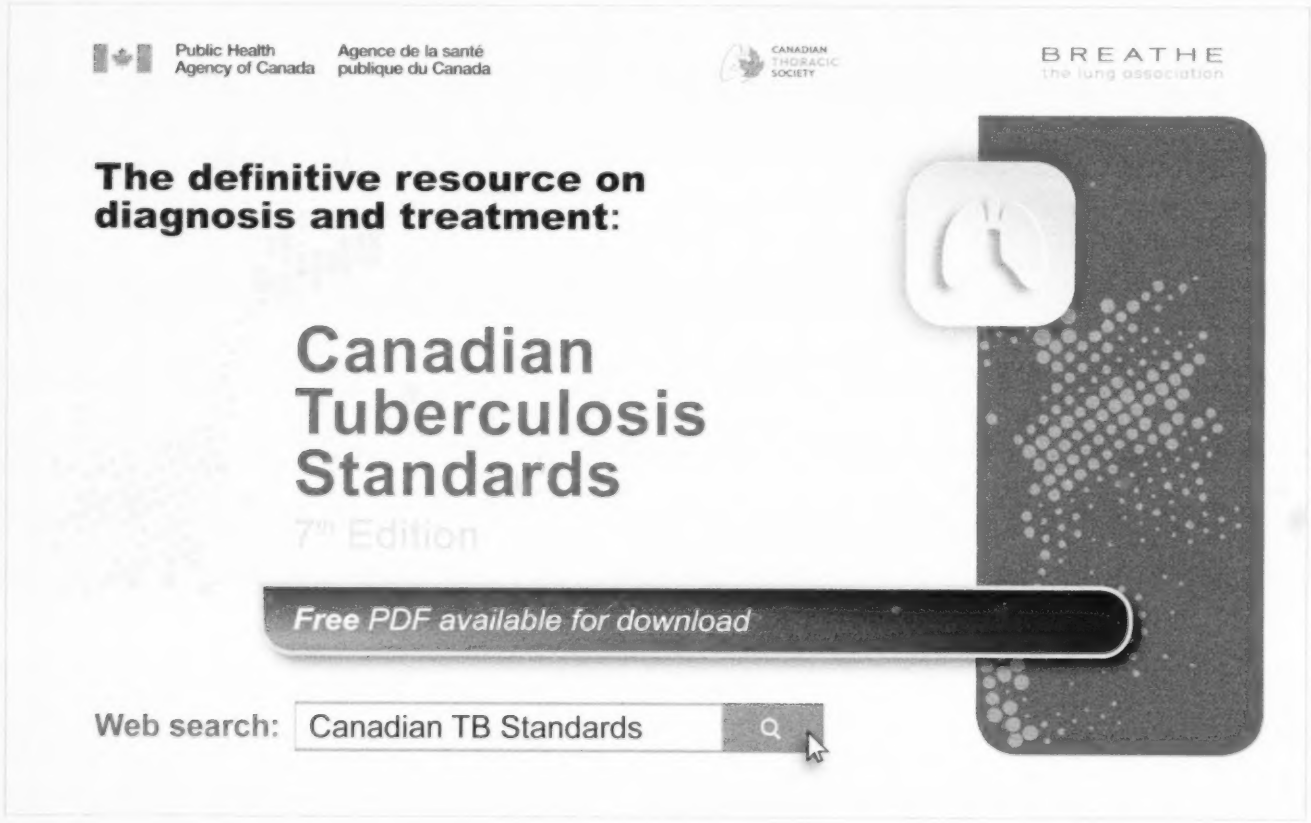

OUTBREAK REPORT

Outbreak of tuberculosis among substance users and homeless people in Greater Montréal, Canada, 2003–2016

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Abstract

Background: In Canada, active tuberculosis (TB) is found mainly among migrants from endemic countries and Indigenous populations. However, cases of active tuberculosis in substance users and homeless persons have been reported in Greater Montréal since 2003.

Objective: To describe the Montréal TB outbreak in terms of the sociodemographic characteristics, risk factors and clinical characteristics of cases, as well as the intensity of public health interventions, the follow-up and identification of locations of potential transmission.

Methods: All cases of active tuberculosis with the same genotype of interest residing in Quebec and epidemiologically linked cases were included in the analysis. Data were retrospectively extracted from routine public health investigations. Characteristics of cases were summarized using Excel. Spatial analysis of locations frequented during cases' infectiousness periods was performed.

Results: Between January 2003 and February 2016, a total of 35 cases were identified. Most (86%) were non-Indigenous people born in Canada. Of these, 28 had several risk factors, including substance use (93%), alcohol abuse (64%), homelessness (46%), comorbidities such as HIV coinfection (36%) and advanced stage of the disease. Seven cases without risk factors were all close contacts of cases. Intensity of case management by public health authorities was high. Locations frequented by cases with risk factors included crack houses, shelters and rehabilitation centres in Montréal's downtown core and a residential setting in a suburban area.

Conclusion: TB outbreaks can occur in marginalized Canadian-born urban populations, especially those with substance use. Tailored interventions in this population may be needed for screening, and earlier identification of both latent and active TB and better linkage to care.

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Introduction

Tuberculosis (TB) is a major driver of morbidity and mortality in the world. In 2015, there were an estimated 10.4 million new cases of active TB disease and 1.8 million TB deaths (1). Canada is among the countries with the lowest incidence of TB, reaching an all-time low of 4.4/100,000 in 2014 (2,3). As in most low-incidence countries, TB is concentrated in specific groups—mainly Indigenous populations and migrants from endemic countries. However, outbreaks have been reported in Vancouver, Toronto, Edmonton and Ottawa as well as in several US cities, typically among groups with overlapping risk factors, such as HIV/AIDS coinfection, homelessness, substance use and incarceration (2-11). While data on incidence rates of active TB in these groups are scarce, an incidence of 13.2/100,000 person-year has been reported among the homeless in Montréal (7).

With an overall active TB incidence of 2.9/100,000 in 2014, Quebec has the lowest incidence rates of TB in the country after the Maritime provinces (3). Between 2008 and 2011, 62.7% of cases were identified in migrants, 25.3% in Canadian-born non-Indigenous people and 10.1% in Canadian-born Indigenous people (12). Most cases were from the Greater Montréal area (12).

All active TB cases are reportable by law in Quebec, and treatment of active TB is mandatory, with regional public health departments able to take legal measures to ensure compliance

with treatment (13). After a case is reported by a physician or a laboratory, the public health department initiates an investigation to trace and test contacts and follows up with the patient until treatment is completed.

In 2003, a few cases of active TB disease were linked to the same community-based organization. Later, more patients from underprivileged neighborhoods in Montréal and surrounding areas were identified with active TB disease, with the same genotype and similar risk factors, such as drug use and homelessness. This marked the start of an outbreak that is still ongoing.

The objective of this article is to describe this TB outbreak in terms of the sociodemographic characteristics, risk factors and clinical characteristics of cases as well as the intensity of public health interventions and the follow-up and identification of locations of potential transmission.

Methods

Case identification

In this retrospective population-based investigation, we included all active and confirmed TB cases with the available genotype of interest who were living in the province of Quebec at the time of diagnosis and all probable cases epidemiologically linked to the confirmed cases. Confirmed cases were identified through Mycobacterial interspersed repetitive units – variable number of tandem repeats (MIRU-VNTR) typing or restricted fragment length polymorphism (RFLP). The genotype of interest was an identical 11-band RFLP and the same 12-loci MIRU or the same 24-loci MIRU after 2006 when this technology was available. These specific 12-loci and 24-loci MIRU define the same strain. All *Mycobacterium tuberculosis* strains were cultured and identified at the Laboratoire de santé publique du Québec (LSPQ). The 24-locus MIRU-VNTR genotyping (14) is performed routinely by the National Microbiology Laboratory as part of a collaboration project with the LSPQ since 2012 (although genotyping was performed on a case-by-case basis before 2012).

Data collection

Each regional public health department extracted data collected through their routine case investigations and follow-up files. Anonymized data from Montréal, Laval and Montérégie were pooled for analysis by the Direction régionale de santé publique du Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal (Montréal Public Health).

Variables of interest included sociodemographic characteristics, risk factors, clinical characteristics, follow-up and intensity of public health intervention as well as locations visited during the infectiousness period. Information about risk factors of interest—substance use, alcohol and tobacco consumption, sex work, homelessness, incarceration in the previous two years, comorbidities such as prior episode(s) of active TB, HIV or hepatitis C coinfection and mental health issues—were routinely collected through public health investigation. Clinical characteristics included site of infection, symptoms, test results (chest X-ray and smear positivity), hospitalization, treatment and clinical outcomes. Variables related to public health intervention and follow-up included use of legal measures, such as isolation orders or court orders and intensity of public health intervention. Average intensity of public health interventions during the full course of follow-up was appraised using an ordinal scale designed with public health nurses. The scale was based on the average number of interventions (such as phone calls, visits, etc., to the patient or a health professional in relation to the case) required to complete the investigation, and to ensure compliance regarding isolation and treatment. The scale had four levels of intervention: low (less than one intervention every 4–6 weeks), normal (one intervention every 4–6 weeks), high (one intervention every 2–3 weeks) or very high (one or more interventions per week).

Locations visited by infectious patients collected during case investigation to trace contacts were retrieved from patient files. The infectious periods were estimated for pulmonary and laryngeal TB cases and defined in accordance with provincial and Canadian guidelines (13,14). The period of infectiousness ended when patients were placed in isolation, the standard care for contagious cases.

Data analysis

Descriptive statistics were obtained using Excel 2010 (Microsoft Corp, Redmond, WA). Patients were stratified into two groups depending on whether they displayed at least one risk factor. Unadjusted proportions and means were presented. For patients who had two episodes of TB with the same MIRU pattern (three cases), only the first episode was included in the descriptive analysis because data for second episodes were frequently missing.

Spatial analysis of the locations patients went to during their infectious periods and the spatial aggregation of these locations was performed. All of the locations visited by patients while contagious were included.

Results

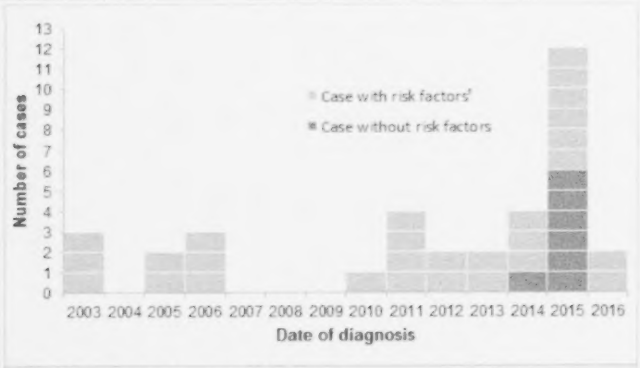
Between January 2003 and February 2016, 35 people met the case definition of this outbreak in three contiguous regions of Quebec: Montréal (21 cases), Montérégie (12 cases) and Laval (two cases). Of these, 29 confirmed cases had the same genotype and six probable cases were epidemiologically linked to cases with this genotype. Three cases had two episodes of active TB with the same MIRU resulting profile for a total of 38 episodes. Two of those cases with a second episode were HIV positive.

Figure 1 displays the epidemic curve for this outbreak. Although there were only eight cases in seven years between 2003 and 2009, the number of cases tripled to 27 from 2010 to 2016.

Sociodemographic characteristics

The age of patients ranged between 1 and 69 years (median 37; interquartile range 33–47); 57% were men. Most (30/35; 86%) were non-Indigenous people born in Canada; three (9%) were Inuit, one (3%) was a non-Inuit Indigenous person and one (3%) was foreign-born.

Figure 1: Outbreak of tuberculosis in Montréal, Montérégie and Laval, 2003–2016


Number of cases
Case with risk factors[1]
Case without risk factors
Date of diagnosis
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016

[1] See Table 1 for type and prevalence of risk factors

Risk factors

Cases were classified in two groups: with risk factors (n=28) and without (n=7). The cases without risk factors were all close contacts (such as family members) of two of the cases with risk factors; four were children under 12 years of age. All of the cases (except one) without risk factors occurred in 2015 and represented half of the cases diagnosed that year (Figure 1).

All cases with risk factors had more than one risk factor. The most common risk factor was substance use (93%), in particular cocaine (54%) and crack (39%) use. Missing data were frequent for some risk behaviours (such as intravenous or heroin drug use, tobacco use and sex work) and mental health issues (**Table 1**).

Table 1: Frequency of risk factors among cases who had one or more risk factors[1] (n=28)

Risk factors	Number (%) of cases with this risk factor	Number (%) of cases without this risk factor	Number (%) of cases with missing values
Substance use	26 (93)	0 (0)	2 (7)
Cocaine	15 (54)	3 (11)	10 (36)
Heroin	3 (11)	5 (18)	20 (71)
Crack	11 (39)	2 (7)	15 (54)
Intravenous drug use	7 (25)	5 (18)	16 (57)
Tobacco use	15 (54)	1 (3)	12 (43)
Alcohol abuse	18 (64)	2 (7)	8 (29)
Sex work	10 (36)	6 (21)	12 (43)
Mental health disorders	8 (29)	5 (18)	15 (54)
Hepatitis C coinfection	12 (43)	11 (39)	5 (18)
Homelessness	13 (46)	15 (54)	0 (0)
HIV coinfection	10 (36)	14 (50)	4 (14)
Non-HIV immunosuppression	5 (18)	18 (64)	5 (18)
Prior incarceration	8 (29)	12 (43)	8 (29)

Abbreviations: n, number; %, percentage
[1] Some do not equal 100% due to rounding to nearest decimal

Clinical characteristics

The most frequent site of active TB disease was the lung (30/35; 86%); five cases had disseminated TB (5/35; 14%). Three patients died before treatment completion, including two who were HIV-positive. Causes of death were substance overdose (n=1), cancer (n=1) and unknown cause that may have been related to TB (n=1). The median age of cases with risk factors was 40 years old (range: 27–57). The median age of cases without risk factors was 12 years old (range: 1–69). **Table 2** presents the frequency of other clinical characteristics and outcomes of cases by risk factor status.

Table 2: Sociodemographic and clinical characteristics of cases by risk factor status[1]

Variables	Number (%) of cases with 1+ risk factor(s) (n=28)	Number (%) of cases without risk factors (n=7)
Sex		
Female	12 (43)	3 (43)
Male	16 (57)	4 (57)
Site of infection[2]		
Pulmonary	24 (86)	6 (86)
Disseminated	5 (18)	0
Laryngeal	1 (4)	0
Other	3 (11)	1 (14)
Symptomatic	26 (93)	4 (57)
Chest X-ray findings		
Normal	1 (4)	1 (14)
Abnormal non-cavitary	11 (39)	5 (71)
Cavitary lesions	12 (43)	1 (14)
Sputum smear		
Negative	2 (7)	6 (86)
1+ positivity	6 (21)	0
2+ positivity	5 (18)	0
3+ positivity	4 (14)	1 (14)
4+ positivity	6 (21)	0
Clinical outcome		
Cured	22 (79)	7 (100)
Still under treatment	2 (7)	0
Lost to follow-up	1 (4)	0
Deceased	3 (11)	0

Abbreviations: n, number; %, percentage
[1] Numbers do not add up to 100% because of missing values (less than 20% for any variable)
[2] Infection categories are not mutually exclusive as some patients had multiple sites of infection. Other sites included lymph node, pleura and abdomen

Cases with risk factors were almost all symptomatic (93%), had advanced disease with X-rays showing cavities (43%), disseminated TB (18%), and high sputum smear positivity (3+ to 4+, 10/28; 35%). Consequently, median duration of hospitalization for cases with risk factors was 38 days (range: 0–571 days) and the median duration of treatment nine months (range: 6–32 months). For cases without risk factors, the median duration of hospitalization was 0 days (range: 0–6 days) and the median duration of treatment six months (range: 6–7 months). Most cases (29/35, 83%) were cured after treatment completion. No antimicrobial resistance before or during the course of treatment was observed (including for cases without risk factors). Cases without risk factors seemed to have less advanced

diseases and included three asymptomatic cases that were diagnosed through contact tracing.

Intensity of public health intervention

There were several factors that lead to a high intensity of public health interventions. In some cases, presentation to health care professionals occurred only when people were at an advanced stage of disease. This meant there had been a long period of infectiousness prior to diagnosis and treatment. This elicited extended contact tracing interventions that uncovered additional cases. Overall, infectiousness lasted between 0.5 and 18.9 months (median: 4 months).

There were also challenges during treatment. Due to medication and isolation compliance issues, eight public health orders and eight court orders were issued to nine patients (26%), mostly to those with risk factors (8/9; 89%). Frequency of intervention by public health nurses was high or very high for 22 cases with risk factors (79%) and for one case without risk factor (14%).

Spatial analysis

Although places frequented by cases were distributed across Montréal, Montérégie and Laval, other locations attended were concentrated in specific hot spots. Shelters, other non-governmental organizations as well as places attended for sex work, recreation and drug use were concentrated in a particular area of downtown Montréal and included the crack houses visited by several cases *(map not shown to respect privacy)*. Spatial analysis of aggregation identified two main hot spots ($P<0.05$): an underprivileged area of downtown Montréal and a residential area in Montérégie.

Discussion

This outbreak investigation shows that TB outbreaks occur in marginalized Canadian-born urban populations, especially among those who are substance users and homeless. The predominant risk factor is substance use, especially crack and cocaine use. Other comorbidities, such as HIV coinfection and mental health issues, were not uncommon. Of concern was the finding that the outbreak had spread to close contacts who had no risk factors other than exposure.

In this outbreak, the number of cases, disease severity, periods of infectivity, comorbidities and disease evolution, were similar to those in previous studies conducted in Montréal (1996–2007) and in BC (5,7). The high rate of HIV coinfection might explain, in part, the advanced stage of active disease and the high number of cases in these populations, as reactivation of latent TB infection is more likely in the immunocompromised (14). Damage to the respiratory tract caused by crack smoking may also contribute to the acquisition and evolution of the disease.

A number of factors might explain the ongoing transmission and duration of this 13-year outbreak. Homeless people, illicit substance users and sex workers often lack health insurance documentation, experience stigma and have competing priorities related to basic needs or substance use that may hinder access to health and social services. This can result in either no health care or delayed presentation for care. In addition, since active TB is relatively rare, clinicians might not consider this diagnosis in non-migrant/non-Indigenous patients. This constellation of factors may have also been at play in other extended outbreaks, an 8-year-long outbreak in British Columbia (6) and a 17-year-long outbreak in Toronto (9). In a review of source patient characteristics at the origin of 26 outbreaks between 2002 and 2011, profiles of high infectivity, social risk factors (alcohol and drug use, homelessness and incarceration) and delay in diagnosis such as those observed in this Montréal outbreak were very frequent (15). Unfortunately, the multiple overlapping risk factors and the long duration of treatment was associated with labour intensive case management, a high level of public health intervention and frequent use of legal measures. Intensive case management also occurred in a similar outbreak in Toronto (4).

Our spatial analysis confirmed previous reports that identified drug use sites as a potential area for transmission (7). A specific area of downtown Montréal is known as a hot spot for drug use with numerous crack houses (16). These are not easy locations for mass screening given the setup, rules and context (17). We also identified a suburban area in the Montérégie linked to one particularly contagious case, possibly identifying a new pattern of substance use that takes place mainly in residential settings (18). Shelters or rehabilitation centers were also visited by several cases over time as reported in Edmonton, where transmission was clearly associated with a small number of shelters (8).

Designing and conducting successful TB control interventions in marginalized urban populations is challenging. Active case-finding in shelters and other community-based organizations between 2013 and 2015 did not identify any new cases, yet additional cases were later found. Concerted efforts continue and include spatial analysis, a new social network questionnaire, public health alerts to clinicians and systematic screening in specific locations. The mobility of this population reinforces the importance of coordination between regions, community organizations and substance use treatment services.

This study had several limitations. First, it used retrospective data to describe risk factors that are routinely but not consistently collected or reported. The questionnaire for case investigation changed over time and varied between regions leading to frequent missing data. Second, we did not report on contact tracing as this information was often difficult to obtain. Third, we used places frequented during the period of infectiousness as proxies of places of transmission. No information was available on places visited when the cases acquired their infection. Some potential locations of transmission were difficult to elicit and some might have been missed. Lastly, some cases linked to the outbreak may have been missed, especially before 2012 when systematic MIRU-VNTR of TB strains began in Quebec. Although 24 loci MIRU-VNTR genotyping offers a high discriminatory power, in rare instances, strains with the same MIRU pattern may not be linked (19).

Conclusion

Although migrants from endemic countries and Indigenous populations remain at highest risk of active TB in Canada, TB outbreaks linked to substance use (especially crack and cocaine) and homelessness occur in urban areas. Marginalized urban people who are substance-users have been identified as a

high-risk group worldwide. This outbreak indicates that a high index of suspicion is needed to detect TB in this population, especially if HIV is present.

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Conflict of interest

None.

Contributions

JA – Conceptualization, Data extraction and analysis, Writing - original draft, review and editing, CL – Conceptualization, Investigation, Data extraction, Writing - Review and Editing, MB – Conceptualization, Spatial analysis, Writing - Review and Editing, DMM – Conceptualization, Data extraction, Writing - Review and Editing, JLS – Conceptualization, Investigation, Data extraction, Writing - Review and Editing, EP – Conceptualization, Data extraction, Writing - Review and Editing, NT – Conceptualization, Investigation, NSi – Writing - Review and Editing, NSa – Writing - Review and Editing, PR – Investigation, Writing - Review and Editing, HS – Laboratory testing, Writing - Review and Editing, MMB – Conceptualization, Investigation, Data extraction, Writing - original draft, review and editing.

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Tuberculosis in Canada - Summary 2015

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Abstract

Background: Tuberculosis (TB) is a global health problem that affects an estimated 10 million people each year. In Canada, the Public Health Agency of Canada (PHAC) monitors active TB disease through the Canadian Tuberculosis Reporting System (CTBRS).

Objective: To report on and analyze the number of new and re-treatment cases of TB in Canada reported for 2015. Results are discussed in the context of previous year's data. Treatment outcomes for cases diagnosed in 2014 are also presented.

Methods: The CTBRS is a case-based surveillance system that maintains non-nominal data on active cases of TB. Data are collected and analyzed by PHAC and validated by each province and territory; no statistical tests were used.

Results: A total of 1,639 cases of active TB disease were reported in 2015, representing a slight increase from the number of cases reported in 2014 (1,614) and a corresponding increase in the incidence rate from 4.5 per 100,000 to 4.6 per 100,000 population. Although the incidence rate of TB remained highest in Nunavut at 119.2 per 100,000 population in 2015, it was nearly half of what it was in 2014. An outbreak in Newfoundland and Labrador resulted in a notable increase in the number of reported cases and incidence rate in this province. In 2015, males accounted for just over half of the reported cases at 53% and older Canadians carried the highest burden of TB with an incidence rate of 10.3 per 100,000 population. Foreign-born individuals continued to account for the majority of reported cases at 71%, but the incidence rate remained highest among Canadian-born Indigenous people at 17.1 per 100,000 population and in particular within the Inuit population at 166.2 per 100,000. Pulmonary TB remained the most commonly reported site of disease. Treatment outcome data for cases reported in 2014 indicated that 85% of cases had been cured or had completed treatment.

Conclusion: Tuberculosis rates in Canada have changed little over the last decade and overall, remain stable and low in the global context. However, foreign-born individuals and Indigenous Canadians continued to be disproportionately represented among reported cases of TB in 2015. As the primary source of national data on TB cases, the data within this report provide timely information for public health action, as well as policy and program development and assessment.

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Introduction

Tuberculosis (TB) is a major global health problem. In 2015 there were an estimated 10.4 million new (incident) cases, for an overall global rate of 142 cases per 100,000 population (1). Although the incidence rate of active TB disease in Canada has been decreasing over time and is among the lowest in the world, high rates persist among Indigenous peoples and among foreign-born individuals (2,3).

The federal health portfolio, in partnership with provincial and territorial governments and other federal departments and agencies, works to address TB in Canada. The Public Health Agency of Canada (PHAC) monitors national active TB disease through the Canadian Tuberculosis Reporting System (CTBRS) which is a collaborative effort with provincial and territorial ministries of health. PHAC uses TB surveillance data to monitor progress toward Canada's goal of preventing and controlling the transmission of TB, as outlined in *Tuberculosis Prevention and Control in Canada: A Federal Framework for Action* (4).

This summary presents a descriptive overview of all reported cases of TB (new and re-treatment) in Canada in 2015 by geographic distribution, age, sex, origin and diagnostic classification. Results are discussed in the context of data from previous years. Treatment outcomes for cases diagnosed in 2014 are also reported.

Previously, these data were published annually in a stand-alone document entitled *Tuberculosis in Canada: Pre-release*. This is the first iteration of this report to be published under a new title, *Tuberculosis in Canada: 2015 Summary*, in the *Canada Communicable Disease Report* (CCDR). Supplementary data are available online (5).

Methods

The CTBRS is a case-based surveillance system that maintains non-nominal data on people diagnosed with active TB disease in Canada. Details on the CTBRS's methods, including data collection processes, data management, data quality control, analysis, and the classification and categorization of population subgroups have already been described (2). In short, provincial and territorial public health authorities voluntarily submit data on all new and re-treatment cases of active TB disease that meet the Canadian case definition for national surveillance (5). Treatment outcome data are submitted between 12 and 18 months following the submission of the initial case report. If treatment is ongoing at the time of data submission to PHAC, the reporting jurisdiction submits an interim report followed by subsequent annual updates until the case file is closed.

Data are submitted to PHAC either through manual completion of a standard reporting form or by electronic transmission. All raw data (paper forms and electronic datasets) are retained in compliance with the *Directive for the collection, use and dissemination of information relating to public health* (Public Health Agency of Canada. 2013 *unpublished document*).

The "incidence rate" refers to the number of individuals diagnosed with active TB disease (new and re-treatment) per 100,000 population in each reporting year. Population denominators used to calculate rates are derived from several sources. Rates for the total Canadian and provincial/territorial population counts by age and by sex are based on mid-year estimations from 2011 census data and are produced by the Demography Division of Statistics Canada (*unpublished data*). The foreign-born population counts are estimated from the 2011 household survey (6). For Indigenous population groups, First Nations, Inuit and Métis, rates are also based on data from the 2011 *National Household Survey* (7). Finally, the rates for First Nations with status, on and off-reserve, were calculated using population projections produced by Indigenous and Northern Affairs Canada (*unpublished data*).

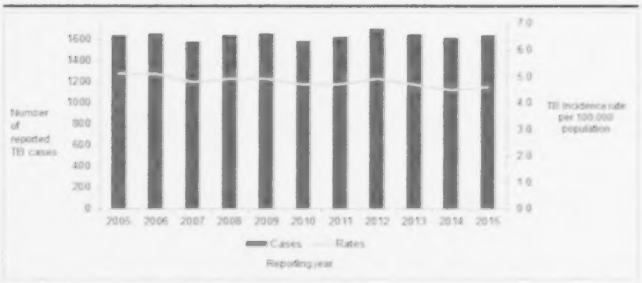
Microsoft Excel 2010 and SAS Enterprise Guide (SAS EG) v5.1 software were used for data cleaning and analysis. No statistical procedures were used for comparative analyses, nor were any statistical techniques applied to account for missing data. Except for risk factor data, data collected through this system are very complete. Data in tables with small cell sizes (n=<5) were not suppressed, since disclosure is not deemed to pose any risk of identifying individual cases. These procedures are in line with the PHAC's *Directive for the collection, use and dissemination of information relating to public health* (*unpublished document*). The data were vetted by the provinces and territories to ensure accuracy.

Data for this report were extracted from the CTBRS in August of 2016. Tuberculosis cases are counted by the date that the reporting jurisdiction confirmed the individual had TB. Because data at the national level are submitted annually, any updates are typically submitted 12 months following the initial annual submission.

Results

In Canada, 1,639 cases of active TB disease were reported in 2015, representing a slight increase from the number of cases reported in 2014 (1,614) and a corresponding increase in the incidence rate from 4.5 per 100,000 to 4.6 per 100,000 population (**Figure 1**, Supplementary Table 1A [5]). Of the cases reported in 2015, 92% (1,509) were identified as new cases. Six percent (101) of the cases were reported as re-treatment cases and previous history of TB disease was unknown for two percent (29) of reported cases (*data not shown*).

Figure 1: Number of reported active tuberculosis cases (new and re-treatment) and incidence rate per 100,000 population in Canada, 2005 to 2015



Geographical distribution

In 2015, the TB incidence rates in the Maritime provinces (New Brunswick, Nova Scotia and Prince Edward Island), Ontario and Quebec were equal to or below the Canadian rate of 4.6 per 100,000 population (**Figure 2**). The incidence rates in all other provinces and territories were higher than the Canadian rate.

Figure 2: Tuberculosis incidence rate per 100,000 population by province/territory in Canada, 2015

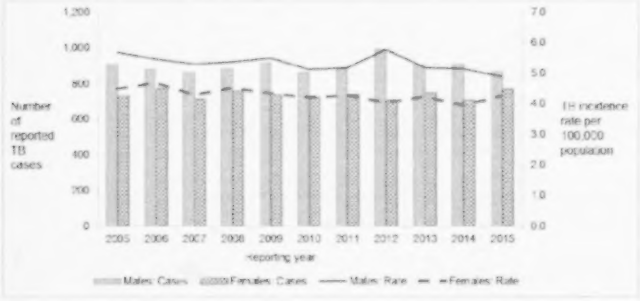
Nunavut continued to have the highest incidence rate of TB at 119.2 per 100,000 population, a rate which was 26 times higher than the overall Canadian rate. However, this incidence rate was nearly half of what it was in 2014 at 232.8 per 100,000 population. Because of a TB outbreak, the number of cases reported in Newfoundland and Labrador rose from seven in 2014 to 33 in 2015, resulting in a fivefold increase in the incidence rate

of TB in this province (6.3 vs. 1.3 cases per 100,000 population). Additional data are available in Supplementary Table 1A (5).

Sex and age distribution

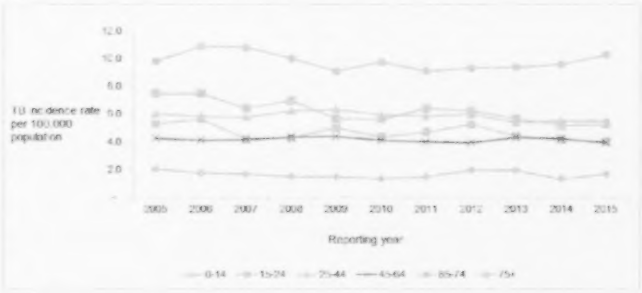
In Canada, between 2005 and 2015, males have consistently accounted for a larger percentage of reported cases than females with correspondingly higher incidence rates (**Figure 3**). In 2015, males accounted for 53% (871) of reported cases, corresponding to an incidence rate of 4.9 per 100,000 population. In comparison, females accounted for 47% (768) of all reported cases for an incidence rate of 4.2 per 100,000 population (Supplementary Tables 1B and 1C [5]).

Figure 3: Number of reported active tuberculosis cases (new and re-treatment) and incidence rates per 100,000 population by sex in Canada, 2005 to 2015



Between 2005 and 2015, TB incidence rates have remained stable or have declined slightly across all age groups (Supplementary Table 2 [5]; **Figure 4**). The most noticeable decrease in incidence rates has been in individuals 65 to 74 years of age, ranging from a high of 7.5 per 100,000 population in 2005 to a low of 5.2 per 100,000 population in 2014. As in previous years, in 2015, older adults (75 years and over), carried the highest disease burden with an incidence rate of 10.3 per 100,000 population. See additional data in Supplementary Table 2 (5).

Figure 4: Tuberculosis incidence rates per 100,000 population by age group in Canada, 2005 to 2015

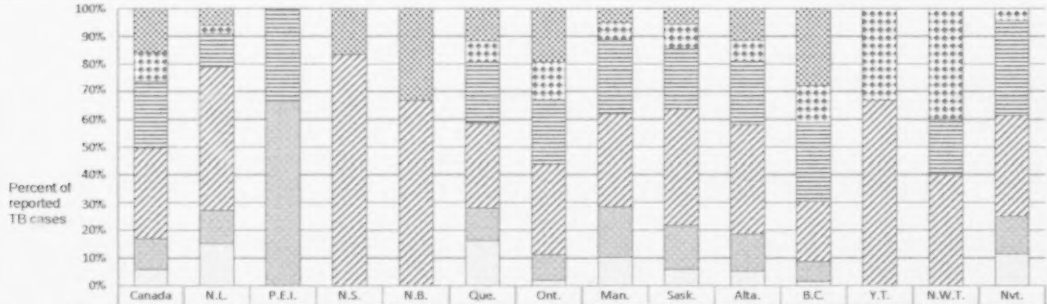


In 2015, individuals aged 25 to 44 years continued to represent the largest percentage of reported cases at 33% (535) (**Figure 5**) and six percent of all reported cases (97) were in children under 15 years of age. Tuberculosis disease in very young children often indicates recent transmission (8) (Figure 5). In Manitoba, Nunavut, Newfoundland and Labrador, and Quebec, over 10% of reported cases were children less than 15 years of age (Figure 5, Supplementary Table 3 [5]).

Distribution by origin

Foreign-born individuals and Canadian-born Indigenous people continued to be disproportionately represented among reported cases of TB in 2015 (**Figure 6**). The foreign-born population, which represented approximately 22% of the total Canadian population in 2015, accounted for 71% (1,169/1,639) of all reported cases corresponding to an incidence rate of 14.8 per 100,000 population. Canadian-born Indigenous people made up approximately five percent of the total Canadian population in 2015 but accounted for 17% (281/1,639) of all reported

Figure 5: Distribution of active tuberculosis cases (new and re-treatment) by age group and province/territory and Canada overall, 2015

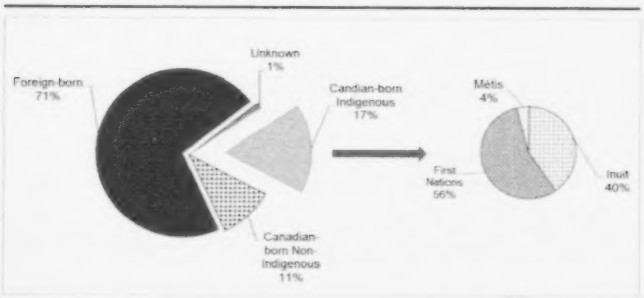


	Canada	N.L.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	Y.T.	N.W.T.	Nvt.
75+	15.7	6.1	0.0	16.7	33.3	11.8	19.2	5.1	5.8	11.4	28.0	0.0	0.0	0.0
65-74	10.6	3.0	0.0	0.0	0.0	7.7	13.8	6.3	8.7	7.6	13.0	33.3	40.0	4.5
45-64	24.0	12.1	33.3	0.0	0.0	22.0	23.4	26.6	21.7	22.9	28.7	0.0	20.0	34.1
25-44	32.6	51.5	0.0	83.3	66.7	30.5	32.4	33.5	42.0	39.5	21.5	66.7	40.0	36.4
15-24	11.2	12.1	66.7	0.0	0.0	11.8	9.2	18.4	15.9	13.3	7.3	0.0	0.0	13.6
0-14	5.9	15.2	0.0	0.0	0.0	16.3	2.0	10.1	5.8	5.2	1.5	0.0	0.0	11.4

Abbreviations: Alta., Alberta; B.C., British Columbia; Man., Manitoba; N.B., New Brunswick; N.L., Newfoundland and Labrador; N.S., Nova Scotia; Nvt., Nunavut; N.W.T., Northwest Territories; Ont., Ontario; P.E.I., Prince Edward Island; Que., Quebec; Sask., Saskatchewan; Y.T., Yukon

cases, with a corresponding incidence rate of 17.1 per 100,000 population. Canadian-born non-Indigenous people accounted for the lowest percentage of reported cases at 11% (170/1,639), for an incidence rate of 0.6 per 100,000 population. Origin was unknown for 1% (19/1,639) of reported cases (**Figure 6,** Supplementary Table 4 [5]).

Figure 6: Distribution of active tuberculosis cases (new and re-treatment) by origin, Canada, 2015



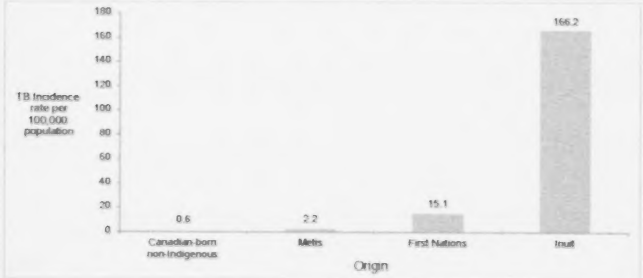
The distribution of TB cases across origin groups varied by province and territory. In Manitoba, Newfoundland and Labrador, the north (Northwest Territories, Nunavut and Yukon) and Saskatchewan, most cases were Canadian-born Indigenous people. In Alberta, British Columbia, the Maritime provinces (New Brunswick, Nova Scotia and Prince Edward Island), Ontario and Quebec, most reported cases were foreign-born. In New Brunswick and Quebec, approximately 30% of reported cases were Canadian-born non-Indigenous people. For the remainder of the provinces and territories, Canadian-born non-Indigenous cases represented fewer than 10% of reported cases (Supplementary Table 4 [5]).

Indigenous peoples

Canadian-born Indigenous people comprise three distinct populations: First Nations, Inuit and Métis. In 2015, of the 281 reported Canadian-born Indigenous cases, 56% (156) were First Nations, 40% (113) were Inuit and four percent (12) were Métis (Figure 6).

In 2015, compared to the incidence rate of 0.6 per 100,000 population in the Canadian-born non-Indigenous population, the incidence rate among the Métis (2.2 per 100,000 population) was almost four times higher and the incidence rate among First Nations (15.1 per 100,000 population) was 25 times higher. The highest incidence rate across all origin groups was among the Inuit at 166.2 per 100,000 population, a rate which was over 270 times higher than the rate in the Canadian-born non-Indigenous population (**Figure 7**).

Figure 7: Tuberculosis incidence rate per 100,000 population by origin, Canada, 2015



Foreign-born cases by region and country of birth

In 2015, there were 1,169 foreign-born cases of TB reported in Canada which represents an incidence rate of 14.8 per 100,000, nine times higher than the rate in the Canadian-born population (1.6 per 100,000 population).

Based on their country of birth, foreign-born cases were grouped into one of nine epidemiological regions as defined by the STOP TB Partnership/World Health Organization (9). Of the 1,169 foreign-born TB cases in 2015, 42% (495) were born in the Western Pacific Region and 26% (303) were born in south-east regions of Asia. Most foreign-born cases diagnosed in Canada are in people whose birth country is considered by the World Health Organization to be a high-burden TB country. Approximately 60% of all foreign-born cases were born in the Philippines, India, China, Vietnam and Pakistan (data not shown). In 2015, the highest incidence rate at 41.5 per 100,000 population was among individuals born in the region of Africa with a high HIV prevalence (Supplementary Table 4 [5]).

Diagnostic classification

Active TB disease is classified as either respiratory or non-respiratory. Respiratory TB includes pulmonary TB, TB of the pleura and TB of the intrathoracic or mediastinal lymph nodes, larynx, nasopharynx, nose and sinuses. Primary disease, a disease state characterized by pleuritis and pleural effusion (usually in an adolescent or young adult, but possibly in any age group, due to recent [within preceding 24 months] infection with *M. tuberculosis* complex) is also captured under the respiratory classification. Non-respiratory TB refers to all other disease sites.

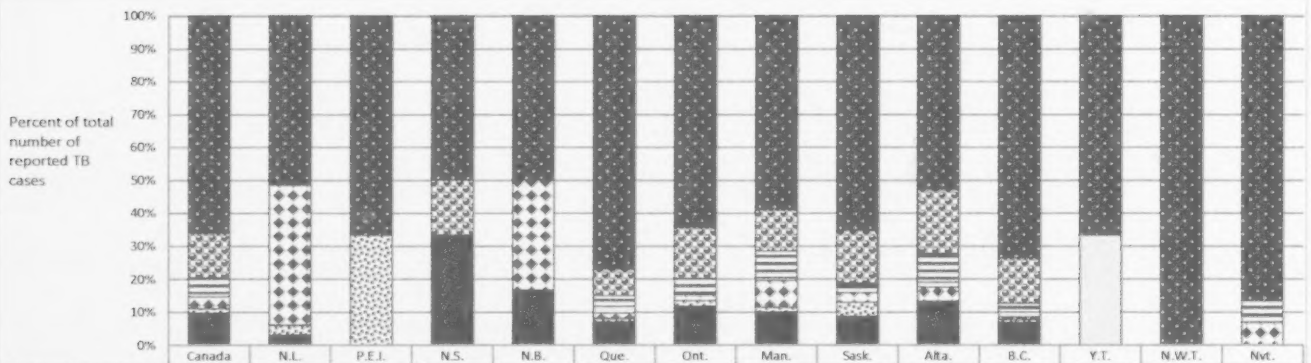
Between 2005 and 2015, respiratory disease accounted for 76% (13,745/17,975) of all diagnosed TB cases in Canada (Supplementary Table 5 [5]). In 2015, 66% of reported cases were diagnosed with pulmonary TB. Pulmonary disease was the most frequently reported diagnostic classification in all provinces and territories. Peripheral lymph node TB remained the second most frequently reported diagnostic site. Overall, four percent (60) of reported cases were diagnosed with primary TB. However, 42% (14/33) of the cases reported from Newfoundland and Labrador were diagnosed with primary TB (**Figure 8**). See additional data in Supplementary Table 6 (5).

Treatment outcomes for 2014

Details on treatment outcome were available for 97% (1,562/1,614) of all reported cases of active TB disease in 2014 (Supplementary Table 7 [5]). Of the cases for which treatment outcome data were available:

- 85% (1,328) were cured or had completed treatment;
- eight percent (119) died before or during treatment;
- two percent (28) had moved outside of the reporting jurisdiction before completing treatment;
- less than one percent (11) were reported as other (four were non-compliant, three refused treatment, one discontinued due to pregnancy and for the remaining three, "other outcome" was not specified);
- less than one percent (13) were lost to follow-up;
- less than one percent (nine) stopped treatment due to an adverse reaction; and
- three percent (54) were reported as treatment ongoing.

Figure 8: Distribution of reported tuberculosis cases by main diagnostic classification: Canada, provinces and territories, 2015



	Canada	N.L.	P.E.I.	N.S.	N.B.	Que.	Ont.	Man.	Sask.	Alta.	B.C.	Y.T.	N.W.T.	Nvt.
Pulmonary	66.0	51.5	66.7	50.0	50.0	76.8	64.2	58.9	65.2	52.9	73.6	66.7	100.0	86.4
Peripheral lymph nodes	13.5	0.0	0.0	16.7	0.0	8.1	15.6	12.7	15.9	19.5	13.8	0.0	0.0	0.0
Other respiratory	4.7	0.0	0.0	0.0	0.0	3.3	4.5	8.2	1.4	8.6	2.7	0.0	0.0	6.8
Miliary	1.0	0.0	0.0	0.0	0.0	2.0	0.3	0.6	1.4	1.4	1.5	33.3	0.0	0.0
Primary	3.7	42.4	0.0	0.0	33.3	1.6	1.8	8.2	2.9	4.3	0.8	0.0	0.0	6.8
CNS	1.4	3.0	33.3	0.0	0.0	1.2	1.7	1.3	4.3	0.5	0.8	0.0	0.0	0.0
Other	9.6	3.0	0.0	33.3	16.7	6.9	11.8	10.1	8.7	12.9	6.9	0.0	0.0	0.0

Abbreviations: CNS, central nervous system; Alta., Alberta; B.C., British Columbia; Man., Manitoba; N.B., New Brunswick; N.L., Newfoundland and Labrador; N.S., Nova Scotia; Nvt., Nunavut; N.W.T., Northwest Territories; Ont., Ontario; P.E.I., Prince Edward Island; Que., Quebec; Sask., Saskatchewan; Y.T., Yukon

Discussion

The number of TB cases reported annually in Canada has remained relatively stable since 2005, averaging approximately 1,630 cases per year. In 2015, 1,639 cases of active TB disease were reported, representing a slight increase from the number of cases reported in 2014 (1,614) and a corresponding increase in the incidence rate from 4.5 per 100,000 to 4.6 per 100,000 population. Although the incidence rate of TB remains highest in Nunavut, 2015 saw a noticeable decrease in both the number of reported cases and the overall incidence rate. On the other hand, Newfoundland and Labrador experienced a significant outbreak of TB in 2015, resulting in an increase in the reported number of TB cases and a corresponding increase in the overall incidence rate. Continuous monitoring is needed to determine if these changes indicate ongoing trends.

Overall, no changes were noted in the distribution of cases by age group, sex or diagnostic site of disease. In 2015, foreign-born individuals continued to account for most reported TB cases, but the incidence rate remained highest among Canadian-born Indigenous people and in particular within the Inuit population. Pulmonary TB remained the most commonly reported site of disease in 2015 and available treatment outcome data for cases reported in 2014 indicated that 85% of cases had been cured or had completed treatment.

The data in this report are considered provisional and subject to change in future iterations of *Tuberculosis in Canada* surveillance reports. Differences between the data published in this report and the data published in previous national, provincial and territorial surveillance reports may be due to reporting delays or differences in when the data were extracted from the various surveillance databases. The reporting province or territory may update its published data on a more regular basis. Should differences exist between this report and provincial or territorial reports, readers are encouraged to contact the provincial/territorial jurisdiction for clarification.

A few limitations should be considered. Because the CTBRS is a passive surveillance system, it relies on data collected retrospectively from medical and laboratory records as opposed to active case solicitation. As a result, it is difficult to ascertain whether all people with active TB disease are being identified and reported. The World Health Organization estimates, however, that Canada's surveillance system has a case detection rate of 90% with a range of uncertainty of 78% to 100% (1). The accuracy of the data is partially a function of timely reporting and updates to PHAC from the provinces and territories. Some degree of lag does occur (i.e. creating a reporting delay). Like all surveillance data, the data in this report may be subject to occasional coding, reporting and processing errors. Over 95% of data elements are complete for most demographic and clinic data.

Compared with other G7 countries (France, Germany, Great Britain, Italy, Japan and the United States of America) Canada has the second lowest TB rate after the United States of America (1). Annual updates on the number of cases of active TB in Canada and corresponding incidence rates are important in monitoring progress toward the goal of reducing the burden of TB in Canada. As the primary source of national data on TB cases, the data within this report provides timely information for public health action, as well as policy and program development and assessment.

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Conflict of interest

None.

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CPHLN device testing recommendations regarding non-tuberculous Mycobacteria (NTM) contamination in heater-cooler units

Source: Canadian Public Health Laboratory Network Device Testing Working Group (CPHLN DTWG) with consultation from the Infection Prevention and Control Expert Working Group and Health Canada. Canadian Public Health Laboratory Network (CPHLN) Device Testing Recommendations regarding Non-Tuberculous Mycobacteria (NTM) Contamination in Heater-Cooler Units. (The complete document is available at: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/device-testing-non-tuberculous-mycobacteria-contamination-heater-cooler.html)

It is the position of the CPHLN DTWG that testing environmental samples from heater-cooler units for *M. chimaera* is not recommended at this time given the lack of available evidence to suggest its value in determining the risk that individual devices pose.

Laboratory detection of *M. chimaera* in environmental samples collected from heater-cooler units presents numerous challenges, including but not limited to:

1. Methods for sample collection, sample processing, and *M. chimaera* detection in environmental samples from heater-cooler units have not been standardized nor validated.
2. Sensitivity, specificity, limit of detection, and negative and positive predictive value of testing are unknown making it impossible to accurately assess patient risk based on testing for *M. chimaera* from heater-cooler units.
3. The patient safety risks associated with removing heater-cooler units from service for prolonged periods while waiting for environmental mycobacterial test results, and thereby delaying the initiation of surgical procedures deemed urgent, likely exceed the risk of *M. chimaera* infection.
4. The paucity of available data regarding growth and viability of *M. chimaera* in heater-cooler units.
5. The inability to determine the efficacy of decontamination procedures for heater-cooler units through testing.

These recommendations are similar to those of the U.S. Food and Drug Administration (FDA) and others and may evolve as new information becomes available. Any such changes will be made in the complete document.

CCDR Call for submissions

The Editorial team of the *Canada Communicable Disease Report* (CCDR) is pleased to announce that the journal has passed the scientific review for PubMed Central and will soon have the capacity to send full-text articles to PubMed.

We invite interested authors to submit papers to CCDR on the surveillance, prevention, detection and mitigation of infectious diseases. Papers can either be targeted at upcoming theme issues, or in addition to the theme of an issue.

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Here are the submission deadlines for future theme issues:

June 12, 2017	Climate change and infectious diseases
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We regularly publish articles in addition to those on the theme.

We welcome submissions in either French or English of original research, systematic reviews, outbreak reports, implementation science reports (describing innovative projects or policies), commentaries, and notes from the field (e.g. first-hand accounts). All papers undergo a double-blind peer-review. We have checklists for authors that match our peer-reviewer forms for many of these types of articles. See our Information for Authors (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/17vol43/dr-rm43-1/assets/pdf/17vol43_1-ar-06-eng.pdf) for submission requirements.

Questions? Contact the Editor-in-Chief: patricia.huston@phac-aspc.gc.ca.

Markers that may differentiate active from latent TB

Source: Lee JY, Jung YW, Jeong I, Joh JS, Sim SY, Choi B, Jee HG, Lim DG. Immune parameters differentiating active from latent tuberculosis infection in humans. Tuberculosis (Edinb). 2015 Dec;95(6):758-63. doi: 10.1016/j.tube.2015.08.003. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26520601.

Tuberculosis remains a highly prevalent infectious disease worldwide. Identification of the immune parameters that differentiate active disease from latent infection will facilitate the development of efficient control measures as well as new diagnostic modalities for tuberculosis. Here, we investigated the cytokine production profiles of monocytes and CD4(+) T lymphocytes upon encountering mycobacterial antigens. In addition, cytokines and lipid mediators with immune-modulating activities were examined in plasma samples ex vivo. Comparison of these parameters in active tuberculosis patients and healthy subjects with latent infection revealed that, active tuberculosis was associated with diminished Th1-type cytokine secretion from CD4(+) T cells and less augmented inflammatory cytokine secretion from monocytes induced by IFN-γ than that in latent tuberculosis infection. In addition, a higher plasma concentration of lipoxin A4 and lower ratio of prostaglandin E2 to lipoxin A4 were observed in active cases than in latent infections. These findings have implications for preparing new therapeutic strategies and for differential diagnosis of the two types of tuberculosis infection.

Author correction for Can Commun Dis Rep. 2016;42(1)

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Suggested citation: Pernica JM. Author correction for Can Commun Dis Rep. 2016;42(1). Can Commun Dis Rep. 2017;43(3):84.

Upon the request of the corresponding author Jeffrey M Pernica, on March 2, 2017 the following addition was made to the article What happened to enterovirus D68 infections in 2015? (1) by Harris D, Desai S, Smieja M, Rutherford C, Mertz D, Pernica JM originally published on January 7, 2016.

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Reference

1. Harris D, Desai S, Smieja M, Rutherford C, Mertz D, Pernica JM. What happened to enterovirus D68 infections in 2015? Can Commun Dis Rep. 2016;42(1):9-11. Available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/16vol42/dr-rm42-1/ar-02-eng.php.

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